NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2004

PLAN FOR HIV-RELATED RESEARCH

V: VACCINES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Vaccines

SCIENTIFIC ISSUES

Safe and efficacious vaccines to prevent HIV infection and disease and/or transmission are essential for global control of the AIDS pandemic. As a result of increased funding from NIH in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued. Basic research in vaccine design and studies of immune responses in small animals and nonhuman primates (NHP) as well as vaccine product development are being pursued. Recent studies in HIV/AIDS vaccine research in animal models have provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional candidate vaccines into clinical testing. Although production of candidate vaccines for clinical study has proceeded slowly for some candidate vaccines, at least 10 new candidate vaccines will enter Phase I trials in the next 2 years. Several new combinations of products, which are expected to provide even better immune responses in combination, will also be tried in Phase I or II trials. Viral vector or DNA vaccine strategies, which utilize the host cells to produce virus proteins in a vaccinated animal, have been able to decrease the initial peak of virus and/or the level of the virus that was established within a few months after challenge. These vaccine strategies appear to have a common ability to induce, at least to some level, cytotoxic T lymphocytes (CTL) that can kill virus-infected cells and T helper cell (Th) responses.

Most test vaccines in the animal models for AIDS have not been effective in preventing virus infection. However, their ability to control viral load early in the course of virus infection and/or the ability to reduce viral load

over a prolonged period may be an equally important public health outcome. This is true for two reasons: From studies of large numbers of infected individuals, the ability to control viral load early in infection is correlated with good prognosis and delayed progression to AIDS. In addition, several studies recently have demonstrated that uninfected partners of HIV-infected subjects become infected far less frequently when there is a reduced level of HIV in the blood. Transmission is also reduced for infants born to HIV-infected mothers whose viral load is low. If HIV vaccines are able to control viral load and thus reduce transmission, they could have a profound impact on the epidemic. This would be particularly true if HIV vaccines can be delivered to individuals with high-risk behaviors including youth and infants that are breast-feeding. The mechanisms of virus control are complex and appear to involve several components of the innate and adaptive immune response, and may vary in individuals depending on their genetic makeup. From animal studies of vaccines and the parallel studies in HIV-infected individuals, multiple immune effector mechanisms, including CTL, Th cells, antibody and secreted chemokines, can each contribute to suppression of viral levels, and it is increasingly likely that there will be no single correlate of immune protection. Thus it is likely that the most effective combination will require multiple component vaccines and evaluation in multiple populations.

SCIENTIFIC ISSUES IMPACTING BASIC RESEARCH IN VACCINE DESIGN AND TESTING

Vaccine Designs

Several vaccine approaches in Phase I or II trials focus on non-envelope proteins. In particular, several trials are exploring vaccines that produce HIV gag proteins, because they are genetically conserved across many clades or subtypes of HIV-1. HIV *tat* or *nef* or other regulatory proteins, as targets for early immune intervention, are under investigation at several research centers. Additional approaches seek to achieve expression or presentation of multiple HIV antigens to maximally stimulate the immune response. The inherent flexibility of DNA vaccines would be a strong advantage, if immunogenicity can be improved. Because the vaccine design is intimately tied to the potential to induce a protective immune response, new approaches are attempting to optimally engage multiple components of the immune response against multiple viral antigens. Combinations of two or more kinds of vaccine approaches and approaches that utilize vectors to target dendritic cells and the sequence of priming and boosting now are being explored more extensively.

Vaccine candidates now are being constructed based on isolates from many regions of the world. Data continue to accumulate both from infected individuals and from vaccinees that there is substantial cross-clade reactivity,

particularly at the cellular level for HIV gag and other relatively conserved proteins. It also is not clear that the genetically defined clade is more important than some other phenotypic or conformational characteristic as the focal point of the vaccine design where envelope proteins are involved. To avoid selection of an HIV-1 isolate representative of distal or unique genetic branch point by randomly selecting a single individual, several of the vaccines entering trials are utilizing genes that are based on consensus sequences where viruses from other clades are of interest. To further improve these vaccine designs, investigators have altered the viral gene sequence to optimize the DNA codons so that they are most efficiently transcribed and translated into proteins when being expressed in mammalian cells.

Structure of the HIV Envelope

Studies of the HIV envelope structure and virus neutralization have led to the concept that there is a transient form of the virus envelope that forms when CD4 binds to the gp120 protein, which makes the virus susceptible to neutralization. Other studies of the structure and function of the HIV envelope have led other researchers to pursue vaccine designs that delete or modify specific carbohydrate sites in the HIV envelope protein, directly exposing hidden or internal protein sites that also appear to make the virus more susceptible to neutralization. Envelope gp120 and gp140 proteins of simian immunodeficiency virus (SIV) and HIV, where variable regions with extensive glycosylation have been deleted, are currently under study in macaques. These modified proteins appear to be more immunogenic and induce high titers of antibody that can neutralize at least some primary HIV isolates. Proteins of this type are expected to enter trials within the next 2 years. With this same goal of inducing broadly neutralizing antibodies, new approaches to configure fully native trimeric gp160 and partially truncated or modified gp140 HIV proteins also are underway. Many of these studies to identify more immunogenic forms of HIV envelope are using envelope genes that are derived from CCR5-using nonsyncytium-inducing isolates that appear to have some advantage either for transmission or for early outgrowth in HIV-infected individuals. In addition, several groups are exploring mixtures of envelope proteins either from different isolates and clades or from combinations of the genes of different HIV envelopes.

Targeting Antigen Presentation with Vectors and DNA Approaches

Use of vectors and adjuvants to enhance the antigen presentation of HIV antigens may be essential to engage the optimal immune responses to virus and virus-infected cells. Several newer vaccine strategies are targeting the

dendritic cells either through vaccine delivery systems or the use of viral vectors that do so naturally. The alphavirus family, which includes Venezuelan equine encephalitis virus (VEE), Sindbis virus, and Semliki Forest virus, may have a natural propensity to move to or be taken up by antigen-presenting cells—dendritic cells or macrophages. Making vaccines that use the outer coat of an alphavirus to carry copies of several HIV protein genes has been shown to induce cellular immune responses that result in reduced virus load in macaques challenged with pathogenic virus. Other investigators have developed DNA vaccines that have incorporated nonmethylated CpG motifs that appear to also target dendritic cells through Toll-like receptors causing a cascade of enhanced cytokine stimulation and Th or CTL induction. In addition, vaccine candidates containing cytokines or other biological immune stimulators have been shown to reduce viral load after challenge in macaque models.

Animal Model Development

HIV-1 does not infect and cause sustained high levels of replication with disease development in any species of NHP without alterations in its genome and adaptation to the host. Thus surrogate models for testing HIV vaccines have been developed. SIV has genes very similar to HIV-1 and HIV-2 and various isolates cause immunodeficiency and susceptibility to opportunistic illnesses. Several chimeric viruses constructed with an envelope gene of HIV-1 and the core and replication genes of SIV (i.e., SHIV viruses) have been produced and adapted for growth in macaque models with differential pathogenicity. A SHIV chimeric virus (SHIV 89.6) that can readily infect both macrophages and T cells is highly pathogenic for peripheral T cells in the macaque. This virus now has been used to challenge the protection provided by a number of vaccine approaches. Concerns have arisen that the early and severe depletion of CD4 cells in this model does not reflect HIV disease in humans. In addition, the apparent ease of protection that is seen in this model may not correlate with the level of protection by the similar vaccines in models with different pathogenicity characteristics. A more recently developed chimeric virus, SHIV-SF162, appears to be selectively macrophage-tropic using the CCR5 co-receptor. SHIV-SF162 has shown a rapid pathogenic loss of T cells in the gastrointestinal tract with a slower loss of peripheral CD4 T cells. Like SHIV 89.6P, several other SHIV chimeras with strong T-cell tropism result in the dramatic rapid depletion of peripheral T cells. Attempts to create new SHIV viruses that can express the envelope gene from HIV isolates of different genetic clades are being developed for the evaluation of vaccines that are based on envelope products from different regions of the world. Clade C SHIV strains based on African or Chinese isolates are being tested in macaques.

Correlates of Immune Protection

Although previous studies in animals have suggested several different correlative markers for immune protection, there still are no clearly defined markers that appear to be consistent across different systems and models. Additional efforts need to seek out assays to measure what makes unique individuals either resistant to virus to which they are exposed or able to control virus rapidly and prevent disease progression. Exposed individuals that have remained seronegative despite high risk of HIV exposure have been documented in groups of individuals that have been studied in various parts of the world. Opposing concerns have been raised about the possibility of a hidden virus infection or the presence of partially attenuated viruses that may become apparent if the repeated exposure either continues giving an opportunity for a more pathogenic recombinant virus to form, or if risk exposure ceases and a protective immune state wanes so that the individual is no longer protected. Sensitive virological and immunological assays need to be applied to studies in these individuals. Then we must develop vaccines that can induce protective responses on a repeatable basis.

Individuals and animals treated with passive immunotherapy or antiretroviral therapy within days to weeks after infection have contributed important information about the complexity of the immune response that may be needed for effective vaccine protection. Studies of long-term survivors of HIV infection have indicated that T-cell help for maintenance of HIV-specific CTLs, CTLs themselves, and chemokines generated by T cells may be extremely important for effective control of viral load. Parallel assessment in animal models has indicated that a complex of these adaptive immune responses will be important immunological endpoints for HIV vaccine trials.

Clinical Trials and International Trial Site Development

The HIV Vaccine Trials Network (HVTN) has expanded from a small number of sites conducting Phase I and II trials to a global network of sites with development of sites in the Caribbean, South America, Thailand, and Africa. Data from the most recent Phase II trial, which examined a particular combination of vaccines (the ALVAC 1452 vector with genes for gag, protease, envelope and epitopes in *tat* and *nef* from Aventis was studied with and without boosting by a dual HIV gp120 protein from VaxGen), did not generate adequate specific cellular immune responses to go forward with a larger trial assessing correlates of protection and efficacy. The trial is continuing to evaluate specific immune responses and to compare these with the cellular immune responses measured by an assay for interferon

gamma that could be conducted on frozen cells. Sites in the Caribbean and South America are conducting a trial in parallel with the U.S.-based study to examine responses in different ethnic and risk populations. It is anticipated that several new vaccine candidates will be starting for Phase I trials, and many of the vaccine trials sites will be enrolling volunteers in a Phase II trial with a DNA vaccine for gag from Merck starting in the second half of 2002. There are new sites in Africa and the Caribbean that will be involved in this next Phase II trial. In addition, the group at the Department of Defense and the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored HVTN are exploring possibilities of close collaborative efforts to conduct parallel efficacy trials in Thailand in populations with different risk patterns with slightly different vaccine products that contain components appropriate to address the clade E that is the predominant HIV-1 clade found in the Thai populations.

In summary, many new vaccine concepts are being explored at the basic and preclinical research levels that are bolstered by new scientific findings on the immune response to HIV and new insights that have been revealed from the structure and function relationships of the HIV virion itself. To be certain that this kind of scientific base continues to fill the gaps in HIV/AIDS vaccine research, the following priorities for AIDS-related research were identified.

FY 2004 PRIORITIES FOR HIV/AIDS VACCINES

NHP Resources for AIDS Vaccine Testing

In considering the various obstacles and the priorities for HIV/AIDS vaccine development, one of the foremost priorities for testing candidate vaccines continues to be a resolution of the crisis in the supply of monkeys available for HIV/AIDS vaccine studies. The supply of NHP, particularly rhesus macaques, for AIDS research and other areas of biomedical research remains a major problem for NIH-funded investigators. Both the supply of animals and the available space for conducting experiments that require adequately controlled biosafety housing are limiting and impeding exploration of new concepts in HIV/AIDS vaccines. Development of additional reagents for evaluation of immunological responses is needed to enable investigators to use alternative models.

PRIORITY FOR FUTURE RESEARCH:

- **NIH must continue to develop expanded access through multiple approaches to NHP for studies of HIV/AIDS vaccines. Wherever possible, investigators should be encouraged to develop models that will employ alternatives to rhesus macaques of Indian origin. Studies of pathogenesis, microbicides, and titrations of new and existing virus stocks for vaccine challenges should be explored in cynomologous macaques, pigtailed macaques, and rhesus of other Asian origins. Collaborative studies and new reagent development should be supported in these additional species to enable comparison of different vaccine and microbicide approaches and avoid duplicative experiments.**

Development of Novel Approaches to Induce Antibodies to HIV Envelope

Several novel approaches to induce broader and more effective neutralizing antibodies against the HIV-1 envelope are being evaluated in investigator-initiated research. Because this problem is clearly complex and may be resolved by several approaches or combined approaches, the resources should be developed to hasten these materials to clinical trials. The production of these products for expanded preclinical studies in animals and in clinical studies in humans often requires special resources (e.g., such as protein production and purification under GMP [good manufacturing production]) to which academic investigators have limited access.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should work with investigators, who are developing novel approaches to induce broadly cross-reactive antibodies against HIV-1 envelope, to ensure that there is minimal lag time between testing in small animals and testing in human clinical trials. Promising vaccine candidates that induce neutralizing antibodies against primary HIV isolates should be advanced as rapidly as possible into comparative testing that will independently evaluate the approaches. This may include outsourcing to obtain additional central resources, developing new facilities that can produce GMP grade proteins or other products with a timely turn-around, and/or fostering academic-private sector partnerships.**

Investigation of the Impact of HIV Clade Differences for Vaccines

Despite extensive evidence that, at the cellular immunity level, there is broad cross-clade reactivity, particularly for conserved HIV proteins and

even some cross-subtype reactivity, some groups have argued that all HIV/AIDS vaccines must be matched to the locale where the vaccine will be tested and delivered. There is little evidence that this is the limitation of current vaccine concepts that already are in clinical evaluation or for new concepts that are being developed. Because there appear to be differences between some responses generated in vaccinees and HIV-infected individuals, many of these issues will not be resolved without evaluation of responses in large-scale trials. There are additional data that suggest a substantial degree of cross-reactivity at the antibody level if appropriate immunogens could be developed. These issues of cross-clade serological responses may be evaluated in NHP models with the development of bridging assays and reagents.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should systematically examine the clade specificity issue for HIV vaccines in clinical studies both in the United States and in international sites where appropriate comparative immunogenicity and efficacy evaluations can be conducted. This requires careful studies of vaccinee responses against a panel of HIV isolates that will provide appropriate material to evaluate cross-clade reactions. To enable these studies, standardized assays, quality assurance, and quality control of panels of reagents that would be used in testing in both preclinical and clinical studies should be developed. In addition, infrastructure to enroll and study the immune responses of populations of vaccinees in multiple countries in multiple trials, including efficacy trials, must be developed to resolve these issues.**

Identification of High-Risk Populations, Particularly in Youth at Highest Risk for HIV Transmission

The changing nature of the HIV/AIDS epidemic, both in the United States and in the international arena, increasingly indicates that young persons, including adolescents, are often the groups at highest risk for HIV transmission. There have been limited studies in both domestic and international sites that have engaged youth in any kind of HIV studies. It will demand particular focused efforts to engage these individuals who are at highest risk in vaccine studies in an ethical and effective manner.

PRIORITY FOR FUTURE RESEARCH:

- **NIH should support studies to identify populations of young people where the risk of HIV transmission is high. The youth in these populations should be engaged as soon as possible in culturally sensitive education efforts about vaccines and vaccine trials. Ongoing information exchange should be developed to ensure that accurate, reliable, and trusted information sources are available for multiple prevention modes in these populations. Recruitment efforts should be poised to address and resolve ethical and legal concerns related to informed consent in this vulnerable population.**

Training and Capacity Building in International and Domestic Vaccine Trial Sites

Trained investigators in HIV vaccines and the conduct of clinical trials are often limiting resources in many of the populations that should be engaged in HIV/AIDS vaccine trial efforts. While physical infrastructure may take only a rapid infusion of money, the training of local personnel for conducting vaccine trials is prolonged and may need specialized training that is not available in standard clinical settings.

PRIORITY FOR FUTURE RESEARCH:

- **Because the lead time is substantial for training personnel and developing vaccine trials infrastructure in most developing countries as well as some underserved populations in the United States, NIH should invest now in training activities that will develop trained investigators that will have links to the communities in which HIV vaccines will be tested. This should include training and education for the broad range of expertise that is essential for the conduct of vaccine trials.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES:

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific and antigen-nonspecific cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure-function relationships and the antigenicity and immunogenicity of HIV proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active and passive immunity.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structure and antigenicity to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by MHC class I and class II molecules. Investigate the interaction of HIV proteins with antigen processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and related viral antigens, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants and enhanced modes of HIV and related lentivirus antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out translational research in NHP and human vaccinees.
- Determine how chronic infection with one strain of HIV or related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain; define the properties of the virus and of the immune system that are responsible for lack of disease induction by attenuated viruses and protection from challenge with wild-type virus; and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, particularly HIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.

- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection from HIV-infected or highly exposed but seronegative individuals, across the life span, and from lentivirus models that will provide the basis for further design of candidate vaccines by conducting the following research:

  - Study acutely infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.

  - Elucidate the functional mechanisms for protective immunity against HIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.

  - Investigate the sequence of events required for mucosal transmission/infection of HIV and other lentiviruses at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.

  - Study mucosal immunity to viral antigens and other infectious pathogens in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.

  - Explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for laboratory studies; and acquire appropriate epidemiological information to enable interpretation of these analyses.

- Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy on viral shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across life span) and protected animals by undertaking the following research activities:

  - Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.

  - Develop improved methodologies and assays to measure viral neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary isolates.

  - Develop and standardize immunological reagents; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, and shipping samples that will be essential in large-scale trials.

  - Study the function of CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary virus isolates; and make available those reagents required for vaccine-related studies.

  - Develop or improve sensitive quantitative measures of HIV (and simian immunodeficiency virus [SIV]) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE - B:

Design viral antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernment organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

STRATEGIES:

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other strategies to target DCs;

- Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
- Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
- Cell surface components carried on the viral surface.

- Foster collaboration between academic investigators, industry sponsors, NIH, the U.S. Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should
  - Enable production of pilot lots of vaccine candidates for testing in NHPs and human subjects;
  - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
  - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration between, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include
  - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different components of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase breadth of immune responses.

- Support design, development, and incorporation of methods to improve or modulate immune responses (qualitatively or quantitatively) in vaccine approaches, including
  - Novel adjuvants and delivery methods that might enhance effective DC antigen presentation;
  - Agents that stimulate or modulate mucosal immune responses or other host defenses, including cytokines or chemokines;
  - Vaccines formulated with cytokines or incorporating cytokine genes in vectors or other biologically active molecules; and
  - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on vaccine responses.
- Evaluate the efficacy of vaccine and other immune prevention strategies in animal models of HIV and related lentiviruses by
  - Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
  - Determining *in vitro* correlates of an *in vivo* protective immune response;
  - Determining the effect of vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious virus challenge on the effectiveness of the vaccine-induced immunity;
  - Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, long-term followup of disease progression with low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
  - Determining the impact of genetic factors and age on vaccine responses and on protection against virus at various challenge sites;
  - Studying the efficacy of the immune response in the face of viral mutation and variation; and

- Investigating vaccines and other biomedical prevention strategies with attention to potential co-factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the mucosal surface or the inductive ability of vaccines.

- Support development of reagents and standardized methods to assess specific vaccine-induced immune responses in animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization and those due to viral infection;
  - Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in animal models;
  - Standardizing and validating assays to assess vaccine potency; and
  - Standardizing and validating assays to be used as Phase III study endpoints.
- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development
  - Whose production utilizes human-derived tumor cell and other continuous cell lines;
  - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - That might have the ability to be generated as either replicating or nonreplicating vectors;
  - That have the potential to cause autoimmunity or highly immunogenic anti-vector responses; or
  - That over-express potentially deleterious vector proteins.

OBJECTIVE - C:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES:

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant animal models of maternal-fetal and maternal-infant perinatal transmission that can
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations;
    - Determine the best immunization routes or protocols to induce antibodies in milk and other secretions;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breast-feeding transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of antiviral drugs in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes

        - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what viral factors are associated with differences in perinatal transmissibility;
        - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervico-vaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission; and
        - Determining if virus in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
    - Identify maternal and infant immune responses that might control viral replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
    - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV with its receptors and co-receptors and/or to target infected cells.
    - Characterize the transmitted viral strains and monitor changes that may occur in proposed trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
    - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:

- Identify and characterize the important issues to consider in the development of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria should include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.
- Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breast-feeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study viral isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- Study the impact of early antiviral therapy and HIV vaccines, given while on effective antiretroviral therapy, on the maintenance or regeneration of antiviral immune responses of HIV-infected infants.

OBJECTIVE - D:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

STRATEGIES:

- Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following tasks:
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of ethnic and racial minority populations affected by HIV and be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger "proof of concept" or efficacy trials.
- Develop a comprehensive plan for conducting vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by
    - Evaluating HIV vaccine candidate efficacy against infection, disease, and/or transmission;

- Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity;
- Ensuring that trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
- Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
- Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.

- Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
- Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III trials and assist in providing solutions.
- Conduct behavioral risk assessment research during vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in a vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

OBJECTIVE - E:

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

STRATEGIES:

- Identify and develop potential domestic and foreign sites with a high seroincidence and access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by studying HIV incidence in cohorts of individuals with high-risk behavior to identify and monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and capable participants in vaccine trials.
  - Develop new laboratory diagnostic tools that can be adapted for high throughput to study new HIV infections and allow distinction between vaccinees and infected individuals.
  - Analyze major histocompatibility complex (MHC) genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected persons representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.

- Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials, development of laboratory infrastructure, standardization of assays, and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of AIDS vaccine efficacy trials. This includes the following:

  - For all vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

  - Develop mechanisms through CABs to engage collaboration and to provide education and the means to inform communities on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

  - For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct vaccine trials adhering to the highest ethical and scientific standards.

- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a research trial. This includes the following research:

- Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of vaccine efficacy.
- Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the epidemic is expanding disproportionately.
- Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to adolescents and young persons that are engaging in high-risk behaviors.
- Collaborate with other HHS agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with Walter Reed Army Institute of Research (WRAIR), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in the international setting.
- Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual intergration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where vaccine trials are conducted.
- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for vaccine efficacy trials.

- Explore innovative trial designs to improve efficiency of vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant negative couples at high risk or discordant couples). This includes the following areas of trial design research:

- Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
- Consider the impact of early antiretroviral therapy on HIV infections in complex trial designs.
- Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs; integrate research on vaccines against opportunistic infections, as appropriate.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2004 OAR
Planning Group for Vaccines

FY 2004 VACCINES PLANNING GROUP

Non-NIH Participants

Margaret A. Liu, M.D., Co-Chair
Senior Advisor in Vaccinology
Bill and Melinda Gates Foundation

David Berger, R.N.
Clinic Coordinator/Research Nurse
Fred Hutchinson Cancer Research Center
University of Washington

Deborah L. Birx, M.D.
Director
U.S. Military HIV Research Program
Walter Reed Army Institute of Research

Susan Buchbinder, M.D.
Principal Investigator
San Francisco Department of Public Health
HIV Vaccine Trials Network

Ms. Karen Charron
Johns Hopkins University Center for Immunization Research

Farley R. Cleghorn, M.D.
Assistant Professor of Medicine and Epidemiology
Institute of Human Virology
University of Maryland

Thomas M. Folks, Ph.D.
Chief
HIV and Retrovirology Branch
Centers for Disease Control and Prevention

Matthew Bidwell Goetz, M.D.
Chief
Infectious Diseases
Greater Los Angeles Healthcare System
Veterans Administration

Alan Greenberg, M.D., M.P.H.
Chief
Epidemiology Branch
Division of HIV/AIDS Prevention
Centers for Disease Control and Prevention

Zimra Israel, Ph.D.
Project Leader
HIV Vaccine Discovery
Wyeth Lederle Vaccines

Ira Longini, Ph.D.
Professor
Department of Biostatistics
Rollins School of Public Health
Emory University

Marta L. Marthas, Ph.D.
Assistant Adjunct Professor
California Regional Primate Research Center
University of California, Davis

John McNeil, M.D., M.P.H.
Department Director
Division of Retrovirology
Walter Reed Army Institute of Research

J. Lawrence Miller, Ph.D.
Executive Director
Black Educational AIDS Project

Mr. William Snow
AIDS Vaccine Advocacy Coalition

Indresh Srivastava, Ph.D.
Associate Director
Chiron Corporation

Mr. Dennis Torres
Fred Hutchinson Cancer Research Center
HIV Vaccine Trial Unit
University of Washington

Carol Weiss, M.D., Ph.D.
Medical Officer
Immune Regulation
Division of Viral Products
Office of Vaccines Research and Review
Center for Biological Evaluation and Research
U.S. Food and Drug Administration

NIH Participants

Bonnie J. Mathieson, Ph.D., Co-Chair
Health Scientist Administrator
Chair
HIV/AIDS Vaccine Coordinating Committee
Office of AIDS Research, NIH

James A. Bradac, Ph.D.
Chief
Preclinical Research and Development Branch
Vaccine and Prevention Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases, NIH

Kenneth Bridbord, M.D., M.P.H.
Director
Division of International Training and Research
Fogarty International Center, NIH

Mary Carrington, Ph.D.
Principal Scientist
IRSP-HLA Typing
Science Applications International Corporation
National Cancer Institute, NIH

Jorge Flores, M.D.
Chief
Vaccine Clinical Research Branch
Division of AIDS
National Institute of Allergy and Infectious Diseases, NIH

Vanessa Hirsch, D.M.V.
Section Head
Laboratory of Infectious Diseases
National Institute of Allergy and Infectious Diseases, NIH

Margaret I. Johnston, Ph.D.
Assistant Director for HIV/AIDS Vaccines
Division of AIDS
Associate Director
Vaccine and Prevention Research Program
National Institute of Allergy and Infectious Diseases, NIH

John Mascola, M.D.
Deputy Director
Dale and Betty Bumpers Vaccine Research Center
National Institute of Allergy and Infectious Diseases, NIH

Nancy Miller, Ph.D.
Preclinical Research Section and Development Branch
Vaccine and Prevention Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases, NIH

William E. Paul, M.D., Ph.D.
Chief
Laboratory of Immunology
Division of Immunology Research
National Institute of Allergy and Infectious Diseases, NIH

George Pavlakis, M.D.
Head
Human Retrovirus Section
Basic Research Laboratory
Division of Basic Sciences
National Cancer Institute, NIH

Jane P. Peterson, Ph.D.
Program Director
Large Scale Sequencing
National Human Genome Research Institute, NIH

Jerry Robinson, Ph.D.
Director for Primate Centers
Comparative Medicine
National Center for Research Resources, NIH

Audrey S. Rogers, Ph.D., M.P.H.
Epidemiologist
Pediatric, Adolescent, and Maternal AIDS Branch
National Institute of Child Health and Human Development, NIH

APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CIPRA	Comprehensive International Programs for Research on AIDS
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
ddI	dideoxyinosine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GBV-C	GB virus (hepatitis G)

GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria
GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission

N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization
NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NMAC	National Minority AIDS Council
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
OPHS	Office of Public Health and Science
PBMC	peripheral blood mononuclear cell
PCP	*pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trial
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis

Th	T helper cells
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WRAIR	Walter Reed Army Institute for Research